IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF NEW YORK

NOVARTIS VACCINES AND DIAGNOSTICS, INC., NOVARTIS PHARMA AG, and GRIFOLS WORLDWIDE OPERATIONS LIMITED,	)	
Plaintiffs,	)	Case No. 18-cv-2434 (DLC)
v.	)	
REGENERON PHARMACEUTICALS, INC.	)	
Defendant.	)	

REGENERON'S RESPONSIVE *MARKMAN* BRIEF
REGARDING ADDITIONAL CLAIM TERMS

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Regeneron Pharmaceuticals, Inc. ("Regeneron") respectfully submits this responsive *Markman* brief on the three disputed claim terms of Claim 17 of U.S. Patent No. 5,688,688 (the "'688 Patent").

I. INTRODUCTION

Plaintiffs ("Novartis") filed this lawsuit asserting the '688 Patent against Regeneron's cell line for producing aflibercept (EYLEA®) and ziv-aflibercept (ZALTRAP®) (together "aflibercept"). Aflibercept is a novel fusion protein consisting of selected portions of three different human proteins; it was invented and patented by Regeneron's scientists in the late 1990s. Novartis's current effort to expand the scope of the '688 patent—a patent which focuses exclusively on nucleic acids from the Human Immunodeficiency Virus ("HIV"), HIV polypeptides, and their use for diagnostic purposes—is contrary to that patent's specification and prosecution history.

After the Court's March 20 claim construction ruling, only one claim, Claim 17, remains in this lawsuit. Claim 17 concerns an isolated nucleic acid molecule with certain human cytomegalovirus immediate early region ("HCMV IE1") sequences, an "enhanced promoter," "operably linked" to nucleic acid sequence encoding a "mammalian polypeptide or heterologous mammalian virus polypeptide."

It became clear during expert discovery that the parties dispute the plain and ordinary meaning of three of the terms of Claim 17—"mammalian polypeptide," "enhanced promoter," and "operably linked"—none of which appear in the specification of the '688 Patent. Two of the three terms, "mammalian polypeptide" and "operably linked" were added to the claim in 2007, ***20 years after*** the 1987 application from which Novartis attempts to claim priority was filed. Claim 17 itself, and the limitation to an HCMV IE1 "enhanced promoter" was first introduced in 1995, nearly eight years after the 1987 application was filed.

Notably, Novartis attempted to avoid briefing the current claim construction issues altogether, arguing that they are somehow waived, and that none of the terms requires construction although the parties dispute their scope. Novartis is wrong. It is well-established that "[w]hen the parties present a fundamental dispute regarding the scope of a claim term, it is the court's duty to resolve it." *O2 Micro Int'l Ltd. v. Beyond Innovation Tech. Co.*, 521 F.3d 1351, 1362 (Fed. Cir. 2008); *Eon Corp. IP Holdings v. Silver Spring Networks*, 815 F.3d 1314, 1320 (Fed. Cir. 2016) (court erred by instructing the jury to give terms their plain and ordinary meaning when the parties disputed claim scope). Accordingly, Regeneron respectfully requests the Court adopt its proposed constructions for the three disputed terms:

First, "mammalian polypeptide" is neither recited nor described in the specification. The plain and ordinary meaning of the term controls: "a polypeptide that is found naturally in a mammal." *Genentech, Inc. v. Amgen Inc.*, 1999 U.S. Dist. LEXIS 24268, *41 (N.D. Cal. May 14, 1999. Novartis's litigation-driven construction is designed to capture fusion proteins, like aflibercept—which is not a polypeptide naturally found in a mammal, but a novel fusion of selected portions of different human proteins. During reexamination, by contrast, Novartis specifically told the Patent Office that it was *not* seeking claims to such novel proteins.

Second, "enhanced promoter," consistent with the claims and the specification, is the promoter region of HCMV IE1 having HCMV IE1 enhancer, promoter, and first intron sequences. By contrast, Novartis's construction would limit "enhanced promoter" to the HCMV IE1 promoter and first intron, which cannot be reconciled with the intrinsic record, but is designed to impermissibly ease Novartis's infringement burden.

Third, "operably linked" means arranged in a functional manner, where the enhanced promoter must be arranged with respect to the nucleic acid sequence encoding the polypeptide so

as to direct its transcription in the host cell—that is precisely what a promoter does. Novartis improperly adds a limitation requiring subsequent translation into protein in an effort to avoid anticipatory prior art.

For all these reasons, the Court should adopt Regeneron's construction of these terms.

II. FACTUAL BACKGROUND

A. Procedural History

In March 2018, more than three years after the '688 Patent expired, and after Regeneron's aflibercept had been on the market for nearly seven years, Novartis filed a complaint alleging that Regeneron's aflibercept producing-cell line infringed all 24 claims of the '688 Patent. Following the Court's March 20, 2019 order on claim construction addressing five disputed terms (D.I. 174), only Claim 17, the "isolated nucleic acid molecule" claim, remains pending.

The parties exchanged expert reports on April 5, May 31, and June 28, during which time the three current disputes regarding claim construction emerged. With respect to the term "mammalian polypeptide" in Claim 17, Novartis's expert, Dr. Calame, argued that Regeneron's aflibercept is a "mammalian polypeptide" because the specification purportedly supports mammalian polypeptides that result from engineered fusions of portions of different mammalian proteins (where neither the portions of the polypeptide, nor the combined fusion polypeptide, exist in nature). Ex. 1[1] (4/5 Rpt.), ¶53. Novartis takes this position because aflibercept is a fusion protein, not a protein that naturally occurs in mammals.

As to "operably linked," the parties initially agreed on its meaning. In fact, Novartis's Dr. Calame first applied Regeneron's construction in her April 5 opening expert report. *Id.*, ¶¶10, 55, 58 (discussing "operably linked" as driving transcription). However, the next month, confronted

[1] All exhibit numbers refer to the exhibits attached to the Declaration of Irena Royzman.

with Regeneron's evidence of anticipation through its expert disclosures, Dr. Calame changed course, now claiming that "operably linked" also requires protein expression. Ex. 22 (5/31 Rpt.), ¶58. This course reversal is a transparent attempt by Novartis to avoid anticipatory prior art.

On June 28, in the reply report of Dr. Calame, Novartis, for the first time, also made clear that there is dispute about the meaning of "enhanced promoter" and whether it includes enhancer sequences in addition to the promoter and intron sequences. Ex. 2 (6/28 Rpt.), ¶¶17–22.

On June 10, even before all the claim construction disputes were crystallized, Regeneron raised with Novartis briefing the claim construction of "mammalian polypeptide" and "operably linked" and possibly "enhanced promoter." D.I. 278-5 at 2. Novartis did not respond until June 26 (despite repeated requests by Regeneron) and then claimed that the claim construction disputes were somehow waived. Ex. 3. The parties met and conferred on July 1 and Novartis asked Regeneron to provide a briefing schedule. On July 8, Novartis agreed to brief the claim construction disputes but only based on its proposed schedule, which would delay expert discovery and summary judgment motions by two months. *Id.*

Regeneron raised these issues with the Court on July 12. D.I. 264. Novartis responded to the Court's proposed briefing schedule by resurrecting its argument that the parties' claim construction disputes were waived and should not be decided by the Court (D.I. 268)—the same argument it makes here. D.I. 274 ("Br.") at 9–11. On July 15, the Court ordered briefing.

B. Claim 17 and the Disputed Claim Terms

The only claim that remains at issue in this case is Claim 17 of the '688 Patent, which is reproduced below (with the disputed terms in bold):

> 17. An isolated nucleic acid molecule comprising an **enhanced promoter**, wherein the **enhanced promoter** comprises the human cytomegalovirus immediate early region HCMV IE1 promoter and the first intron proximate to the 3' end of the HCMV IE1 promoter *and wherein the **enhanced promoter** is*

operably linked *to a nucleic acid sequence encoding a* ***mammalian polypeptide*** *or a heterologous mammalian virus polypeptide.*[2]

C. The '688 Patent Specification Solely Concerns HIV, Not Mammalian Polypeptides

The entirety of the '688 Patent concerns HIV and the patent is part of large family of HIV-related patents. *See e.g.*, '688 Patent, Abstract, Technical Field (1:23-28), Background of the Invention (2:27-29), Summary of the Invention (2:60-61). The specification enumerates the contemplated categories of "invention." This list of 12 "aspects of invention" concerns HIV nucleic acids and HIV polypeptides in each instance. *Id.*, 3:1-4:29. Similarly, the originally filed claims did not mention HCMV IE1 sequences or an enhanced promoter. Ex. 29 at 159-168. The same is true of the preceding applications.

Likewise, each example of the '688 Patent concerns HIV, not mammalian, polypeptides. '688 Patent, 14:5-16:15. Only one example (Example 2.3.2) discloses a plasmid with an HCMV IE1 promoter. *Id.*, 27:65-28:45. That one two-paragraph example, also concerns HIV because it discloses a plasmid (pCMV6a) that encodes an HIV protein, gp120. D.I. 174 at 10.

Between 1987 and 1995, Chiron (the original assignee) filed a series of patent applications that all had the same HIV-focused specification with claims directed solely to HIV. *See* diagram below. On August 10, 1994, Chiron filed the application that resulted in the '688 Patent. At that time, all of the claims concerned HIV. Ex. 29 at 159-168. In October 1995, applicants added claim 82 (which became claim 17), reciting an HCMV IE1 "enhanced promoter," and pointed to pCMV6a in Example 2.3.2 as support. Ex. 4 at 5; Ex. 5 at 10.

Novartis first added "mammalian polypeptide" and "operably linked" to Claim 17 in 2007 during reexamination, declaring that "mammalian polypeptides" were well-known as of 1987

[2] The language in italics, reciting two of the three disputed claim terms, was first added in 2007 during reexamination.

and therefore did not need to be described. Ex. 6 at 16-17, 19-20; Ex. 19 at 18, 20. Subsequent to these arguments, the Patent Office issued the reexamination certificate for the '688 Patent in 2009 that included Claim 17 with the new limitation "mammalian polypeptide."

D. The Accused Product

Novartis asserts Claim 17 against Regeneron's stable cell line for production of aflibercept, a novel fusion protein that is engineered from selected portions of three different human proteins (VEGFR1, VEGFR2, and IgG1) and does not exist in nature. The selected portions of genes used to create the fusion gene for aflibercept are not found naturally in any cells, mammals or otherwise, and their combination and arrangement is also nowhere found in nature. The man-made molecule is a product of the ingenuity of Regeneron scientists and is novel and patented. Ex. 7. It was first described in 1999. It did not exist in 1994, much less 1987, the date of invention that Novartis asserts.

III. LEGAL PRINCIPLES OF CLAIM CONSTRUCTION

As *Phillips v. AWH Corp.* instructs, claim terms are generally given their ordinary and customary meaning. 415 F.3d 1303, 1312 (Fed. Cir. 2005) (en banc). The ordinary meaning of a claim term is not "the meaning of the term in the abstract." *Id*. at 1321. Instead, "the 'ordinary meaning' of a claim term is its meaning to the ordinary artisan after reading the entire patent." *Id*.

To construe claims, courts should first look to the intrinsic evidence: the claims, specification, and prosecution history. *Phillips*, 415 F.3d at 1314. The "context in which a term is used" in the claims can be "highly instructive." *Id.* "Because claim terms are normally used consistently throughout the patent, the usage of a term in one claim can often illuminate the meaning of the same terms in other claims." *Id.*

In addition, "claims must be read in view of the specification, of which they are a part." *Id.* at 1315. The specification "is the single best guide to the meaning of a disputed term." *Id.*

"The construction that stays true to the claim language and most naturally aligns with the patent's description of the invention will be in the end the correct construction." *Id.* at 1316.

The prosecution history is also important as the inventor may have "limited the invention in the course of prosecution, making the claim scope narrower than it would otherwise be." *Id.* at 1317. "Any explanation, elaboration, or qualification presented by the inventor during patent examination is relevant, for the role of claim construction is to capture the scope of the actual invention that is disclosed, described, and patented." *Fenner Invs., Ltd. v. CellCo P'ship*, 778 F.3d 1320, 1323 (Fed. Cir. 2015). "The public notice function of a patent and its prosecution history requires that a patentee be held to what he declares during the prosecution of his patent." *Teva Pharm. USA, Inc. v. Sandoz, Inc.*, 789 F.3d 1335, 1344 (Fed. Cir. 2015).

Although "less significant than the intrinsic record," extrinsic evidence such as dictionaries and treatises can assist the Court in determining the meaning of claim language. *Phillips*, 415 F.3d at 1317. Expert testimony may also aid the Court, but expert testimony "is 'not useful' if based on 'conclusory, unsupported assertions,' and should be 'discount[ed]' if 'clearly at odds with . . . the written record of the patent.'" *SkinMedica, Inc. v. Histogen Inc.*, 727 F.3d 1187, 1210 (Fed. Cir. 2013) (quoting *Phillips*, 415 F.3d at 1318).

Consideration of the accused product "provides meaningful context" for the Court's claim construction analysis. *Wilson Sporting Goods Co. v. Hillerich & Bradsby Co.*, 442 F.3d 1322, 1326-27 (Fed. Cir. 2006). Indeed, the Federal Circuit has "emphasized the importance of the context provided by an analysis of the accused device when ruling on claim construction and the problems presented by construing claims in the absence of such context." *Jang v. Boston Sci. Corp.*, 532 F.3d 1330, 1337 (Fed. Cir. 2008).

IV. CONSTRUCTION OF DISPUTED TERMS

A. "Mammalian Polypeptide"

Term	Regeneron's Proposed Construction	Novartis's Proposed Construction
"mammalian polypeptide"	Plain and ordinary meaning: A polypeptide that is found naturally in a mammal	Plain and ordinary meaning: A precursor protein or a complete mature protein or fragment thereof, including portions of, or entire polypeptides of, two or more different mature polypeptides, the sequence(s) for which are of mammalian origin

Regeneron's proposed construction of "mammalian polypeptide" is the plain and ordinary meaning: a polypeptide that is found naturally in a mammal. Novartis's construction, disclosed for the first time in this supplemental claim construction brief, is divorced from the intrinsic evidence. Instead, it is crafted to try to capture Regeneron's novel fusion protein that was created long after the application for the '688 Patent was filed. And critically, Novartis explicitly told the public and the Patent Office that the phrase "mammalian polypeptide" was not intended to cover novel polypeptides (like aflibercept).

1. The Claims and Specification Support the Plain and Ordinary Meaning of Mammalian Polypeptide

The claim language supports Regeneron's construction that "mammalian polypeptide" means "a polypeptide that is found naturally in a mammal." Specifically, Claim 17 uses two distinct and separate terms "mammalian polypeptide ***or*** a heterologous mammalian virus polypeptide." The term "mammalian ***virus*** polypeptide," in contrast to the alternatively claimed "mammalian polypeptide," is a protein from a mammalian virus (a virus that infects mammalian cells), such as HIV. Green Decl., ¶67.[3] It distinctly covers virus polypeptides such as gp120, as opposed to "mammalian polypeptides." Indeed, during reexamination, applicants pointed to gp120 in Example 2.3.2 as a mammalian virus polypeptide. Ex. 8 (Truett Decl. at ¶10); Ex. 6 at

[3] "Green Decl.," refers to the declaration of Michael Green, M.D., Ph.D., filed herewith.

20; Ex. 19 at 19. This disclosure of a mammalian ***virus*** polypeptide, gp120, is the only disclosure of Claim 17. Green Decl., ¶41. As the Court explained in its first Claim Construction Order, D.I. 174 at 37, Example 2.3.2 is "the sole example that describes the claimed invention." Claim 17 does not impart any novel meaning to "mammalian polypeptide." Importantly, it does not refer to any derivatives of mammalian polypeptides or fusion proteins. Green Decl., ¶¶68-69.

In fact, the specification uses the term "fusion protein," not "mammalian polypeptide" or "mammalian virus polypeptide," when referring to a fusion polypeptide, *i.e.*, a man-made non-naturally occurring polypeptide. '688 Patent, 12:39-58 ("fusion protein"), Example 2.5 ("gag-env fusion protein"; a fusion of the HIV gag and env proteins not found in nature), Examples 3.5-3.7 ("fusion protein"). Green Decl., ¶¶68-69. Thus, Applicants knew how to use the term "fusion" when it was appropriate; yet intentionally elected not to claim it in Claim 17.

Regeneron's construction is therefore the plain and ordinary meaning of "mammalian polypeptide." *Verizon Services Corp. v. Vonage Holdings Corp.*, 503 F.3d 1295, 1304 (Fed. Cir. 2007) ("Since the specification does not define the term 'server,' we look to its ordinary meaning to a person of ordinary skill in the art"). Here, the term "mammalian polypeptide" occurs nowhere in the specification (because the language was added in 2007 into the claims); this is not surprising as the entirety of the specification including each example concerns HIV. But the term is well understood by persons of skill in the art, namely that "mammalian" means "of" or found naturally in a mammal. Green Decl., ¶¶65-71; Exs. 9, 10, 11.

The district court's claim construction ruling in *Genentech, Inc. v. Amgen Inc.* is directly on point. 1999 U.S. Dist. LEXIS 24268 (N.D. Cal. May 14, 1999). Just as in this case, the *Genentech* court was asked to construe the term "mammalian polypeptide." The court in *Genentech* found "no express intent" in the patent to "impart a novel meaning" to the term

"mammalian." The court, relying on the plain meaning of the term from Webster's dictionary, ruled that "mammalian polypeptide" means "a polypeptide that is found naturally in a mammal." *Id.* at *41. In doing so, the *Genentech* court expressly rejected a similar construction to the one proposed by Novartis here, stating: "[t]here is not room in this definition for a polypeptide that is similar to, or a derivative of, a polypeptide that occurs naturally in a mammal." *Id.* at *39.

Just as in *Genentech*, the '688 Patent contains no definition of "mammalian polypeptide", nor is there any indication of any intent to apply any novel definition of the phrase (to the contrary, Novartis specifically told the patent office that it did not intend to cover novel polypeptides, *see infra*). And just as in *Genentech*, this Court should apply the plain and ordinary meaning of the word mammalian, and construe the phrase "mammalian polypeptide" to mean "a polypeptide that is found naturally in a mammal."

2. The Prosecution History Confirms that Novel Polypeptides Are Not "Mammalian Polypeptides"

Novartis's own statements to the Patent Office during reexamination of the '688 Patent further support Regeneron's construction. Specifically, Novartis argued to the Patent Office that it did not need to describe any mammalian polypeptides in the specification of the '688 Patent because mammalian polypeptides were well known in the art as of 1987 and because **Novartis was not trying to encompass any novel polypeptides** (such as Regeneron's engineered and novel aflibercept protein). Instead, Novartis relied on the plain and ordinary meaning of "mammalian polypeptide" to obtain claims reciting that subject matter.

Specifically, during reexamination, Novartis argued:

- "[H]ere, where the claim element 'mammalian polypeptide or a heterologous mammalian virus polypeptide' is ***not a novel element*** that has never been characterized, a single working embodiment [gp120] is sufficient to indicate to one of skill in the art that the inventors had possession of the claimed invention." Ex. 6 at 16.

- "In this case, one of skill in the art would have no difficulty in understanding what a 'mammalian polypeptide or a heterologous mammalian virus polypeptide' is ***as neither concept is novel*** to this patent." *Id.* at 17.

- "[I]n *Eli Lilly* the inventors were claiming the recombinant protein insulin which at the time was novel. By contrast, heterologous polypeptides including mammalian polypeptides and mammalian virus polypeptides were ***well known at the time of filing of the present application***." *Id.* at 19; Ex. 19 at 18.

- "The MPEP makes clear, based upon established case law, that information which is ***well known*** in the art need not be described in detail in the specification." Ex. 6 at 20; Ex. 19 at 20.

These statements that Novartis made to get Claim 17 issued confirm that applicants did not intend to impart any novel meaning to the term "mammalian polypeptide" or to encompass subject matter that did not exist and was not well known at the time of filing of the application (*i.e.*, that was novel), such as Regeneron's yet-to-be invented aflibercept. Green Decl., ¶¶65-71, 77-78. Indeed, departure from the ordinary meaning of "mammalian polypeptide" that Novartis presented to the Patent Office would capture polypeptides that are novel or not well known in the art (e.g., engineered polypeptides or derivatives of natural mammalian polypeptides or fusions).

It is well settled that "a patentee's statements during prosecution, whether relied on by the examiner or not, are relevant to claim interpretation." *Fenner Invs.*, 778 F.3d at 1325. Novartis repeatedly declared that it was not claiming novel polypeptides to obtain issuance of Claim 17. The public is entitled to rely on its representations to the Patent Office. *Teva*. 789 F.3d at 1344; *Gillespie v. Dywidag Sys. Int'l, USA*, 501 F.3d 1285, 1291 (Fed. Cir. 2007).

3. Novartis's Construction Is Concocted to Cover the Novel Fusion Proteins It Did Not Describe or Claim

Novartis's construction of "mammalian polypeptide" is litigation driven, and is contrived simply to cover aflibercept, a novel fusion protein that is not found in nature. And notably, this definition does not resemble the one that Novartis presented in Delaware to cover the antibody products at issue in that litigation—products that are ***not*** fusion proteins like aflibercept. Ex. 12

at ¶102 (defining "mammalian polypeptide" as "heterologous polypeptide containing a sequence of at least 15 amino acids, the sequence being found in a mammal").

Specifically, for its construction in this action, Novartis stitches together selected bits ("a complete protein or fragment," "portions of sequences," "two or more different mature polypeptides") from col. 9:19-33 that on their face are not a definition—"polypeptides which ***may*** be a precursor protein …."—and concern different subject matter. Green Decl., ¶72.

Novartis also takes these phrases entirely out of context. To understand these phrases, they have to be read together with the earlier passage which discusses the screening of "proviral DNA in infected cells" with "fragments," and has absolutely nothing to do with "mammalian polypeptides." *See* 9:10-15 ("Of particular interest is employing the region containing the HIV gag or env genes, where ***fragments may be employed to screen proviral DNA in infected cells***, ***to determine the identity of retroviruses*** associated with AIDS or LAS obtained from different human hosts."). It is also purely litigation-driven.

Novartis contends that its definition covers "expressly disclosed embodiments." Br. 14. That is simply false. The sole support for Claim 17 is Example 2.3.2. Green Decl, ¶¶25-43; D.I. 174 at 10, 37. That example discloses a "gp120 polypeptide" with its "gp120 coding region" and no other polypeptide. It makes no mention whatsoever of any mammalian polypeptide or a fusion protein. Novartis is also not helped by the human tissue plasminogen activator ("tPA") signal sequence in that example. tPA is not part of the gp120 polypeptide and not described as such. As the heading of Example 2.3.2 reflects, the example concerns expression of "gp120," a ***viral*** polypeptide. In Example 2.3.2, tPA is merely a ***short segment*** of tPA (the "signal sequence") that brings gp120 mRNA to the right location in the cell to be translated into protein and secreted. The tPA signal sequence is cleaved before the full-length protein is made and it is

not part of the resulting viral gp120 protein. *See* Claims 11 and 12; Green Decl., ¶¶42, 75-76.

Novartis also repeatedly refers to "fusions" and argues its definition "would not exclude fusion polypeptides that incorporate sub-domains of mammalian proteins." Br. 15. But the '688 Patent provides no support for any such fusions, and such fusions are not what is claimed. Notably, as discussed above, the specification uses the term "fusion protein" when referring to a fusion polypeptide rather than a term like "mammalian polypeptide" or "virus polypeptide."

In addition, the only discussion of "fusions" in the file history was during reexamination, when Novartis discussed tPA fused to gp160 or to gp120, which is not a fusion protein as the tPA signal sequence is never part of the final gp160 or gp120 proteins. Ex. 6 at 20 ("exemplification of the recombinant making of HIV polypeptides alone or as fusions…"); *see* '688 Patent at 2:60-65, 23:15, 25:25-29, 12:39-58; Ex. 13 at 9; Ex. 14 at 20. Further, in Examples 2.2.2 and 2.3.1, the inventors describe the tPA in the context of the SV40 promoter, and not the Claim 17 enhanced HCMV IE1 promoter. Green Decl., ¶¶74-76.

Put simply, when Novartis wanted to describe a fusion polypeptide that does not occur in nature, it used the phrase "fusion protein." But it did not use "fusion protein" in Claim 17; it used the phrase "mammalian polypeptide." And it told the Patent Office that it was not covering novel polypeptides that did not exist in 1994 or 1987.

Novartis also erroneously argues that the '688 Patent discloses "mammalian polypeptides" by pointing to unrelated portions of the specification that discuss antibodies and selection enzymes such as dihydrofolate reductase ("dhfr"). Br. 17 (citing to Dr. Calame's declaration); Green Decl., ¶¶79-81. This has nothing to do with Claim 17. There is no suggestion anywhere in the '688 Patent of operably linking the dhfr gene or any antibody encoding sequence to an HCMV IE1 enhanced promoter. *Id.*; Ex. 15 (Truett Tr.) at 84:12–23,

127:3-128:5. The '688 Patent only concerns HIV polypeptides and only discloses the use of HCMV IE1 sequences with gp120, a single HIV polypeptide. Example 2.3.2, the only disclosure for Claim 17, does not disclose a "mammalian polypeptide," nor does it disclose any "mammalian virus polypeptide" beyond gp120. Thus, there is no support for an isolated nucleic acid molecule with an HCMV IE1 enhanced promoter operably linked to a sequence encoding a "mammalian polypeptide." Green Decl., ¶¶41, 79-81.

Finally, Novartis misleadingly argues that Regeneron and its expert have taken contradictory positions. The very passages of Dr. Green's reports that Novartis cites, show that he opined that the tPA signal sequence and fusion virus proteins in the patent are different from the claimed "mammalian polypeptide" – precisely Regeneron's position here. Salman Decl., Ex. 8 at ¶52, Ex. 9, at ¶68; Green Decl., ¶¶65-82. In addition, Novartis's argument that Regeneron contradicts its previous position from its invalidity contentions is incorrect. Br. 15. In its preliminary invalidity contentions, Regeneron stated that Factor VIII was a mammalian protein, not a fusion protein. Factor VIII is a full length, non-fusion protein, despite Novartis's assertion otherwise. Ex. 16, ¶53.

For these reasons, Regeneron respectfully requests the Court adopt the plain and ordinary meaning of the term "mammalian polypeptide" to a person of skill in the art, which is a polypeptide that is found naturally in a mammal.

B. "Enhanced Promoter"

Term	Regeneron's Proposed Construction	Novartis's Proposed Construction
"enhanced promoter"	Plain and ordinary meaning: the promoter region of hCMV IE1 having hCMV IE1 enhancer, promoter, and first intron sequences	Plan and ordinary meaning: a promoter comprising the hCMV 1E1 promoter and the first intron proximate to the 3' end of the hCMV IE1 promoter

The plain and ordinary meaning of "enhanced promoter" is the promoter region having the HCMV IE1 enhancer, promoter and the first intron sequences. Regeneron's construction is based on: (i) the claims of the '688 Patent, (ii) the only relevant description in the specification, and (iii) how a person of ordinary skill in the art would understand the term in view of the intrinsic evidence. Novartis, by contrast, proposes a construction where an "enhanced promoter" can be limited to just the HCMV IE1 promoter and first intron, contrary to the only disclosure of the claim (Figure 29 and Example 2.3.2)— a disclosure that has enhancer sequences *in addition* to the promoter and first intron.

1. The Claims Teach that the Enhanced Promoter Is the Promoter Region

The term "enhanced promoter" appears in Claim 17 as follows: "enhanced promoter comprises the human cytomegalovirus immediate early region HCMV IE1 promoter and the first intron proximate to the 3' end of the HCMV IE1 promoter."[4] Claim 18, a dependent claim, refers to the claimed enhanced promoter of Claim 17 as "**the promoter region**," evidencing that the patentee intended the "enhanced promoter" of Claim 17 to refer to a "promoter region," that included more than just the HCMV IE1 promoter and intron, *i.e.*, that also includes enhancer sequences. *Phillips*, 415 F.3d at 1314 (the usage of a term in other claims illuminates its meaning); *ArcelorMittal France v. AK Steel Corp.*, 700 F.3d 1314, 1320 (Fed. Cir. 2012) ("The claims and specification should be read 'in a manner that renders the patent internally consistent'") (citations omitted).

Claim 22 also indicates that Claim 17 is directed to the "the promoter region." Claim 22 (like Claim 18) references Claim 17 and refers to "**the enhanced promoter region**" being capable of directing the transcription of a polypeptide coding sequence downstream from the

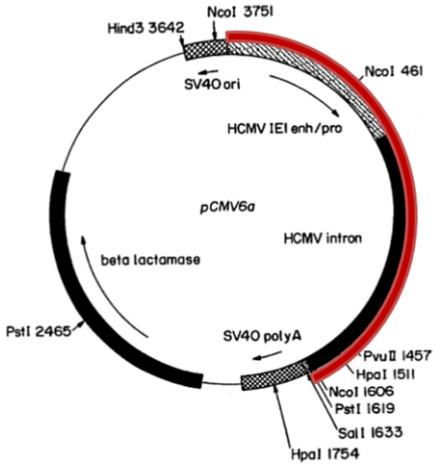
[4] The Court's March 20, 2019 claim construction order construed the plain and ordinary meaning of the term "first intron" as the entirety of the first intron. D.I. 174 at 51.

"promoter region." The use of "***the***" when referencing the promoter region in Claims 18 and 22, which directly reference Claim 17, demonstrates that Claim 17 provides antecedent basis for Claims 18 and 22. Accordingly, "[a] plain reading of the claims shows that the term refers to the [enhanced promoter] earlier described," such that reference to "enhanced promoter" includes the promoter region of HCMV IE1 having HCMV IE1 enhancer, promoter, and first intron sequences. *Eastman Chem. Co. v. Aktiengesellschaft*, 47 F. App'x 566, 573–74 (Fed. Cir. 2002) ("no other construction of the term [at issue] was feasible given that the word 'the' must have an antecedent basis.") (citing *Process Control Corp. v. HydReclaim Corp.*, 190 F.3d 1350, 1356–57, 52 USPQ2d 1029, 1033 (Fed. Cir. 1999) (noting the importance of an antecedent basis in claim construction)).

2. The Specification Makes Clear that the Enhanced Promoter Includes the Enhancer, Promoter and First Intron

The only disclosure in the specification of the '688 Patent relevant to Claim 17 is Example 2.3.2 which describes the "promoter" or "promoter region" of Claim 17 as the 1.7 kbp fragment of pCMV6a ("the HCMV IE1 promoter as a 1.7 kbp Ssp I-SalI fragment"). '688 Patent, 28:39-43. That fragment includes the HCMV IE1 enhancer, promoter and first intron sequences. Green Decl., ¶¶84-91. The same two paragraphs of Example 2.3.2 also describe this same region as the "transcription regulatory region." *Id.*; '688 Patent, 28:17-19. Figure 29 (showing Example 2.3.2) of the '688 Patent likewise depicts the "promoter" or "promoter region" as "HCMV IE1 enh/pro" (*i.e.*, HCMV enhancer/promoter) upstream of the HCMV IE1 intron. Accordingly, Example 2.3.2 and Figure 29 demonstrate that an enhanced promoter includes the enhancer, promoter and first intron sequences of HCMV IE1. *Meds. Co. v. Mylan, Inc.*, 853 F.3d 1296, 1309 (Fed. Cir. 2017) ("it is entirely appropriate to limit the term 'efficiently mixing' to the sole portion of the specification that adequately discloses 'efficient mixing' to the public");

Hologic Inc. v. SenoRx, Inc., 639 F.3d 1329, 1338 (Fed. Cir. 2011) (construing term based on specification, figures and "what the inventors of the [] patent conceived").



'688 Patent, Fig. 29 (annotated in red to show the "enhanced promoter" or "promoter region").

3. The Prosecution History Supports Regeneron's Proposed Construction

The prosecution history also supports Regeneron's proposed construction, *i.e.*, as including the HCMV IE1 enhancer, promoter and first intron sequences. During reexamination, Novartis consistently referred to the "enhanced promoter" as "***compris[ing]"*** the HCMV IE1 promoter and the first intron, not limited to the promoter and intron, as it suggests now. Ex. 6 at 6; Ex. 14 at 12; Ex. 17 at 12; Ex. 18 at 12; Ex. 19 at 8. It is well-established that "comprising" means "including." *CIAS, Inc. v. All. Gaming Corp.*, 504 F.3d 1356, 1360–61 (Fed. Cir. 2007).

4. Novartis Broadens "Enhanced Promoter" Contrary to the Intrinsic Record

Novartis' proposed construction is at odds with the intrinsic evidence. Despite using the term "comprising" in its proposed construction, Novartis nevertheless argues that Claim 17 "***defines***" the "enhanced promoter" as the promoter and first intron, and nothing more, in an attempt to broaden the claim. Br. 22. That is plainly wrong based on the explicit language of the claim. Claim 17 merely states that the enhanced promoter "***comprises***" the promoter and first

intron with the first intron located at the 3' end of the promoter. It does not "define" enhanced promoter as only a promoter and first intron.

The term "enhanced promoter" *includes* the enhancer sequences of the promoter region, in addition to the promoter and first intron sequences. *CIAS*, 504 F.3d at 1360–61 ("comprising" means "including"). Novartis's "definition" is based on improperly conflating "comprising" with "consisting." *SkinMedica, Inc. v. Histogen Inc.*, 727 F.3d 187, 1201 (Fed. Cir. 2013) (rejecting patentee's construction of term that was not a "natural reading" in light of the specification).

Novartis also argues that the term "enhanced promoter" must mean only the promoter and intron because the patentee could have used a different term, "transcription regulatory region," which Novartis acknowledges includes the enhancer sequences. Br. 22. However, a patentee can use different words to describe the same subject matter, as is the case here.[5] There is no indication in the claims or Example 2.3.2 that "transcription regulatory region" covers subject matter different than "enhanced promoter" or "promoter region" or "enhanced promoter region." Notably, the claims state that the transcriptional regulatory region includes the promoter and first intron proximal to the 3' end of the promoter—just as the enhanced promoter. *Compare* Claims 1, 4-5, 9, 13, 15 to Claims 17, 18 and 22. And, Novartis's Dr. Calame explicitly and repeatedly acknowledges that the "enhanced promoter" and "transcription regulatory region" are one and the same: "Claim 17 of the '688 Patent uses 'operably linked' to refer to the functional relationship between the ***HCMV IE transcription regulatory region*** and the polypeptide coding sequence."

[5] *See, e.g., Multiform Desiccants, Inc. v. Medzam, Ltd.*, 133 F.3d 1473, 1480 (Fed. Cir. 1998) ("claims that are written in different words may ultimately cover substantially the same subject matter" and "doctrine of claim differentiation cannot broaden claims beyond their correct scope"); *Pickholtz v. Rainbow Techs., Inc.*, 284 F.3d 1365, 1373 (Fed. Cir. 2002) (two terms have the same meaning where "nothing in the patent itself explicates their relationship or indicates any difference"); *MarcTec, LLC v. Johnson & Johnson*, 664 F.3d 907, 918 (Fed. Cir. 2012) ("the doctrine of claim differentiation cannot broaden claims beyond their correct scope").

D.I. 275 ("Calame Decl."), ¶30; *see also id.* at ¶35.

Novartis's construction also disregards the specification and prosecution history. As discussed above, in order to obtain allowance of Claim 17, applicants relied on pCMV6a as "sufficient" support for all the pending claims (including claim 82, which issued as Claim 17). Ex. 4 at 5; Ex. 5 at 10; D.I. 174 at 14. pCMV6a has the enhancer, promoter and intron sequences. There is no support in pCMV6a, Example 2.3.2 or anywhere else in the specification for broadening Claim 17 through claim construction to only require a promoter and intron and to avoid the enhancer sequences of the "promoter region." Further, Novartis's claims that the '688 Patent purportedly provides a "promoter-intron" invention (Br. 22) is a fiction. Nowhere in the specification of the '688 Patent is there any description or suggestion of using only the promoter and first intron without the enhancer sequences of pCMV6a. Green Decl., ¶89. The promoter is not even delineated from the enhancer ("enh/pro" in Figure 29). *Id.* And nowhere in the specification is there any suggestion that the HCMV promoter is "enhanced" by the first intron as Novartis asserts (Br. 24). Green Decl., ¶¶ 93-96. In contrast, the enhancer sequences are well known to increase transcription. D.I. 174 at 5; D.I. 73, ¶29.

Novartis also argues that the prosecution history shows that the "enhanced promoter" is different from the "transcription regulatory region" and therefore that it is not the 1.7 kbp fragment of pCMV6a. Br. 23. The opposite is true. The Examiner stated during prosecution that "from the description in the specification, one of skill in the art would recognize the 'transcription regulatory region' as being the 1.7 kbp fragment of pCMV6a set forth in the specification," but found that claims 63 and 65 confused matters as they claimed the "transcription regulatory region" comprised the "enhanced promoter" and "intron." Ex. 26 at 4. In response to the rejection, applicants cancelled claims 63 and 65. Ex. 5 at 6. Therefore, the

prosecution history supports Regeneron's construction that the term "enhanced promoter" is not part of "the transcription regulatory region," but rather that the two are one and the same.

In sum, Regeneron's proposed construction should be adopted because it is supported by the intrinsic evidence while Novartis's has no support in the intrinsic record.

C. "Operably Linked"

Term	Regeneron's Construction	Novartis's Construction
"operably linked"	Plain and ordinary meaning: Arranged in a functional manner, where the enhanced promoter must be arranged with respect to the nucleic acid sequence encoding the polypeptide so as to direct its transcription in the host cell	Plain and ordinary meaning: Arranged so that the polypeptide is expressed

The parties also dispute the plain and ordinary meaning of "operably linked" in the context of Claim 17. Regeneron's construction, consistent with the plain language of Claim 17 and what a promoter is, makes clear that the "enhanced promoter must be arranged with respect to the nucleic acid sequence encoding the polypeptide so as to direct its transcription in the host cell." In arguing that a promoter that "drives transcription" of a sequence must also necessarily "lead to translation of that sequence" into an expressed protein, Novartis improperly seeks to narrow Claim 17 beyond its plain language in an attempt to avoid express anticipation by prior art. Novartis's construction is improper when, as here, the applicant intentionally elected not to claim "protein expression" in Claim 17. Nothing in Claim 17 requires translation of the transcript into protein, much less as a result of linkage with the promoter.

1. The Claims Teach that an "Operably Linked" Enhanced Promoter Directs Transcription

As with the other two disputed terms, "operably linked" does not appear in the specification. But the language of Claim 17 is "highly instructive" as to how "operably linked" would be understood by a person of ordinary skill in the art. *Phillips*, 415 F.3d at 1314. In

particular, it is the "enhanced promoter" that is "operably linked" to "a nucleic acid sequence encoding a mammalian polypeptide or heterologous mammalian virus polypeptide." As the Court explained, "a 'promoter' region of DNA is a segment of DNA that signals where transcription starts." D.I. 174 at 5; *see also* D.I. 73, ¶29. It directs transcription of the nucleic acid sequence, DNA, into RNA. The enhanced promoter, thus, needs to be arranged in a manner to direct transcription of the nucleic acid sequence once it is in the host cell. Green Decl., ¶98.

The other claims in the '688 Patent that also include "operably linked" further support the proper construction of this term. *Phillips,* 415 F.3d at 1314 ("the usage of a term in one claim can often illuminate the meaning of the same term in other claims."). Specifically, Claims 1, 13, and 15 all use the term "operably linked" with respect to the HCMV IE1 transcription regulatory region. Claim 1, provides that the HCMV IE1 transcription regulatory region "is capable of ***directing the transcription*** of a polypeptide coding sequence operably linked downstream from the transcription regulatory region." Claims 13 and 15 similarly provide that the HCMV IE1 transcription regulatory region directs the "transcription of a polypeptide coding sequence operably linked downstream from the regulatory region." Green Decl., ¶¶99-100. The terms "transcription regulatory region", and "enhanced promoter" are used interchangeably in the claims. In fact, Novartis's Dr. Calame refers to the "enhanced promoter" of Claim 17 as the "HCMV IE1 transcription regulatory region": "Claim 17 of the '688 Patent uses 'operably linked' to refer to the functional relationship between the HCMV IE transcription regulatory region and the polypeptide coding sequence." Calame Decl., ¶30.

Claims 19 and 22 also use the term "operably linked" in substantially the same manner. Both describe "directing the transcription of a polypeptide coding sequence operably linked downstream." *Id.* Claim 22, which references Claim 17 and relies on it for antecedent basis,

states that "**the enhanced promoter region** is capable of directing the transcription of a polypeptide coding sequence operably linked downstream from the promoter region." The claims of the '688 Patent thus evidence that "operably linked" in the context of Claim 17 describes an enhanced promoter that is arranged with respect to the nucleic acid sequence encoding a polypeptide in such a manner that it directs the transcription of the polypeptide coding sequence into RNA once in the host cell. Green Decl., ¶¶98-100; *Fin Control Systems Pty, Ltd. v. OAM, Inc.*, 265 F.3d 1311, 1318 (Fed. Cir. 2001) (it is "presume[d] that the same terms appearing in different portions of the claims should be given the same meaning").

2. The Specification Confirms Regeneron's Construction

The specification is to the same effect. The arrow in Figure 29 above HCMV IE1 enhancer/promoter indicates the initiation and direction of transcription from the enhanced promoter. Green Decl., ¶101. There is no dispute that a promoter directs transcription in the nucleus of a cell; in fact, Novartis explicitly states so (Br. 21). Similarly, Novartis's Dr. Calame states that she "agree[s] with Dr. Green that "[i]n order for the enhanced promoter to be arranged in the nucleic acid molecule so as to function, the promoter must be arranged with respect to the nucleic acid encoding a polypeptide in such a manner that it directs the transcription of the nucleic acid sequence once in the host cell." Calame Decl., ¶39. Translation is a subsequent step that occurs outside the nucleus of the cell and does not involve the promoter. Green Decl., ¶101. Nowhere does Novartis contend—nor can it—that a promoter directs translation of the sequence as that is not what a promoter does.

3. Novartis's Construction Disregards the Claims and Imports an Extraneous Limitation Contrary to Law

Novartis reads in "expression" of protein into Claim 17. Br. 17-21. All of it theories for doing so are predicated on conflating Claim 17 with an expression system, when it is not.

First, Novartis argues that "a good promoter should certainly be 'capable' of ***directing transcription*** but that is a necessary, *yet insufficient*, aspect of the recombinant expression system." Br. 21 (emphasis in original). It argues "that the central purpose of the HCMV promoter-intron expression system [] is to drive expression of the target polypeptide." *Id.* That misses the point. Claim 17 is not directed to a "recombinant expression system" or even to a "vector" or to pCMV6a, the only vector disclosed in the specification relating to the claims. Indeed, all the "vector" and "vector for expression" claims have already been dismissed from this action. D.I. 188.

Second, Novartis is similarly not helped by the title of the '688 Patent ("Vector for Expression of a Polypeptide in a Mammalian Cell"), *see Pitney Bowes, Inc. v. Hewlett–Packard Co.*, 182 F.3d 1298, 1312 (Fed. Cir. 1999) (a patent's title is "near[ly] irrelevan[t]" to claim construction), or the fact that gp120 protein is transiently expressed in COS cells from the pCMV6a vector in Example 2.3.2. Br. 19. Claim 17 does not require expression of protein (nor does it provide for a polyadenylation signal without which production of protein cannot occur); the expression of protein is not the function of a promoter. The purpose and function of the promoter is transcription. That is what a person of ordinary skill in the art would understand and the claims of the '688 Patent reflect. Green Decl., ¶¶98-104.

Finally, Novartis's citations to the prosecution history (Br. 20) are similarly misplaced. The prosecution history excerpts that Novartis cites concerned discussion of the claims directed to "vectors" for expression—not just Claim 17's "isolated nucleic acid molecule." 1/29/1996 Amendment at 8; Ex. 21 at 6 (referring to Claims 17-24); Ex. 20 at 9.

In short, Novartis's proposed construction imports an additional limitation not found in the intrinsic record. It points to no definition or disclaimer requiring such a construction and the

claims, and understanding of a person of ordinary skill in the art, are at odds with Novartis' construction. The Court should adopt Regeneron's proposed construction and reject Novartis'.

V. PARTIES' CLAIM CONSTRUCTION DISPUTES ARE NOT WAIVED

Novartis's waiver argument is meritless. Novartis cannot, and does not dispute, that 1) there is a substantive dispute between the parties as to the scope of three claim terms, as evident by its submission of a full claim construction brief and an expert declaration; and 2) the law requires the Court to resolve the parties' dispute. *Every Penny Counts, Inc. v. Am. Express Co.*, 563 F.3d 1378, 1383 (Fed. Cir. 2009) ("[T]he court's obligation is to ensure that questions of the scope of the patent claims are not left to the jury. In order to fulfill this obligation, the court must see to it that disputes concerning the scope of the patent claims are fully resolved.").

Contrary to Novartis's argument, Regeneron's request for claim construction is not untimely as the dispute only became apparent when expert reports were recently served. *Supra* § II.A. Specifically, on June 10, 2019, more than two weeks ***before*** the parties served their reply experts, Regeneron contacted Novartis about the need for claim construction on at least two and possibly three terms (depending on whether there was a dispute as to the meaning of "enhanced promoter"). Novartis delayed responding for two weeks, and when it finally did respond on June 26, it claimed that claim construction disputes were waived. It then reversed course by proposing a claim construction briefing schedule contingent on delaying its own lawsuit by two months. Because Regeneron refused the delay, the parties submitted letters to the Court regarding claim construction briefing.

In addition, it is well-established that claim construction disputes that arise before trial are not waived. *See, e.g.*, *GPNE Corp. v. Apple Inc.*, 830 F.3d 1365, 1372 (Fed. Cir. 2016) (claim construction disputes that arise before trial are not waived when both parties and the court are aware of the dispute); *Altera Corp. v. PACT XPP Techs. AG*, No. 14-cv-02868-JD, 2015 WL

4999952, at *8 (N.D. Cal. Aug. 21, 2015) (requiring claim construction after expert discovery and motion practice revealed a fundamental dispute after the court had construed the claims).

Here, with service of Novartis's expert reports, it became clear that the parties disputed the scope of three terms such that the parties had to propose additional briefing. Indeed, Novartis proposed a different construction of "mammalian polypeptide" in its previous litigation involving the '688 Patent than what it proposes here. Ex. 12, ¶102. Novartis changed course on the meaning of "operably linked" in this case. *Supra* § II.A. And it only became clear that Novartis was reading out the enhancer sequences of "enhanced promoter" in its reply report served on June 28. *Id*. Indeed, *Wi-LAN*, a case that Novartis relies on (Br. 9-10) recognizes that a district court may use its case-management authority to set a schedule for claim construction. *Wi-LAN USA, Inc. v. Apple Inc.*, 830 F.3d 1374, 1385 (Fed. Cir. 2016) (no abuse of discretion where district court declined to find that new construction was barred). [6]

VI. CONCLUSION

For the reasons discussed above, Regeneron respectfully requests the Court adopt its proposed constructions.

[6] Novartis's cases are inapposite. Its reliance on *Track Innovations* is misplaced because, unlike the plaintiff in that case, Novartis has "changed its interpretation of these terms" such that a "real dispute exists regarding their definition." *On Track Innovations Ltd. v. T-Mobile USA, Inc.*, 106 F. Supp. 3d 369, 384 (S.D.N.Y. 2015). Further, the parties dispute what the plain and ordinary meaning of the terms is, such that *Advanced Steel Recovery* is inapposite. *Advanced Steel Recovery, LLC v. X-Body Equip., Inc.*, No. 2:12-CV-1004-GEB-DAD, 2014 WL 3939356, at *1 (E.D. Cal. Aug. 11, 2014) (court applying the plain and ordinary meaning of terms). Finally, in stark contrast to *Hunter* where claim construction disputes were raised on the eve of trial, Regeneron timely requested further claim construction before expert discovery has closed (and where a trial date has not been set). *Hunter Douglas Inc. v. Great Lake Woods, Inc.*, No. 15-CV-00106-REB-KLM, 2019 WL 1375675, at *1 (D. Colo. Mar. 27, 2019).

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